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Synthesis, antimicrobial activity and molecular modeling study of some new pyrimidine derivatives

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ARTICLE INFORMATION



DOI: 10.5155/eurjchem.6.2.127-130.1175

Received: 27 October 2014

Received in revised form: 26 November 2015

Accepted: 27 November 2015

Published online: 30 June 2015

Printed: 30 June 2015

KEYWORDS

2D NMR

Antibiotics

Pyrimidine

Schiff's bases

Antimicrobial activity

Molecular modeling study

ABSTRACT

Condensation of 2-amino-4-chloro-6-methoxypyrimidine with aromatic aldehydes (2-hydroxy-1-naphthaldehyde, 3,4-dihydroxybenzaldehyde and piperonal) afforded products in good yields. The synthesized compounds (Schiff base of pyrimidine derivatives) were screened for their antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Bacillus subtilis*, *Klebsiella*, *Pseudomonas aeruginosa* and *Salmonella*. Additionally, the compounds were tested for antifungal activity against *Candida albicans*, *Candida tropicalis* and *Aspergillus fumigatus*. All compounds exhibited potent antibacterial and antifungal activity. Molecular modeling studies were performed, showing the hydrogen bindings and hydrophobic interactions.

Cite this: *Eur. J. Chem.* 2015, 6(2), 127-130

1. Introduction

Pyrimidine molecule is a promising structural moiety for drug designing, which form a component in a number of useful drugs and are associated with many biological and therapeutically activities [1].

The diverse array of biological and pharmacological activities of pyrimidines including antimicrobial [2-5], antihypertensive [6], antitumor [7-12], antiviral [13,14], anti-HIV agents [15-17], in addition to their cardiovascular [18,19] and diuretic [20,21] properties. Furthermore, some pyrimidines were used as hypnotic drugs [22], in addition to their activity as calcium-sensing receptor antagonists [23] and as antagonists of the human A2A adenosine receptor [24] as well. Bacimethrin (4-amino-5-(hydroxymethyl)-2-methoxy pyrimidine) (1) is a pyrimidine antibiotic which is active against several *staphylococcal* bacteria (Figure 1) [25,26]. On the other hand, methoprim, 5-(3,4,5-trimethoxybenzyl) pyrimidine-2,4-diamine [27,28] is used, in combination with sulfamethoxazole, as a bacteriostatic_antibiotic (trimoxazole) for the treatment of urinary tract infections and *Pneumocystis*

jirovecii pneumonia [29]. Gemcitabine (2), a pyrimidine antimetabolite, is an approved drug in the U.S. for pancreatic cancer and also in combination for certain lung cancer patients (Figure 1) [30]. Further, monastrol [31] is another model of pyrimidine derivative as inhibitor of kinesin Eg5 that interact with microtubuline and then causes mitotic arrest [32].

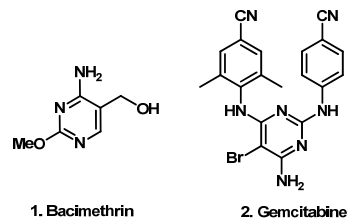
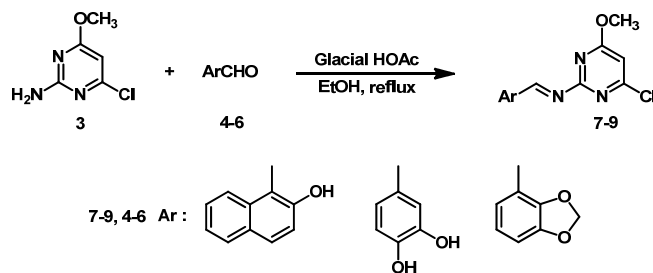


Figure 1. Some potentially active pyrimidine derivatives.

Schiff bases attracted much interest due to their biological properties, especially those derived from heterocyclic analogues and possess cytotoxic [33], antimicrobial [34] and



Scheme 1

other activities. Kalpesh *et al.* [35] have reported several novel Schiff base derived from 2-amino-4,6-dimethoxypyrimidine with various aromatic aldehydes.

The present work describes the synthesis and biological activity of new azomethine compounds derived from 2-amino-4-chloro-6-methoxypyrimidine, in addition to their molecular modeling study.

2. Experimental

2.1. Instrumentation

Melting points were measured by a Philip Harris melting point apparatus and are uncorrected. The IR spectra were recorded in the range 4000-200 cm^{-1} on a Pye-Unicam SP3-300 spectrometer using KBr discs. ^1H , ^{13}C , HSQC and HMB NMR spectra were measured on a Bruker spectrometer at 600 MHz with TMS as an internal reference.

2.2. Synthesis

2.2.1. General procedure for the synthesis of aryl-1-(4-chloro-6-methoxypyrimidin-2-yl)imine derivatives (7-9)

2-Amino-4-chloro-6-methoxypyrimidin (3) (160 mg, 1.0 mmol) and aromatic aldehydes (1.1 mmol) 4-6 were dissolved in absolute ethanol followed by addition of catalytic amount of glacial acetic acid drop wise and the mixture was heated under reflux for 8 h. The reaction mixture was then cooled in an ice bath and the crude product thus obtained was collected by filtration, further purified by recrystallization from ethanol (Scheme 1).

1-(((4-Chloro-6-methoxypyrimidin-2-yl)imino)methyl)naphthalen-2-ol (7): From *o*-hydroxy-naphthaldehyde 4 (189 mg). Yield: 242 mg (77%). M.p.: 214-218 °C. FT-IR (KBr, ν , cm^{-1}): 3400 (OH), 3070, 3067 (CH-Aro.), 2930 (CH-alip.), 1631-1558 (C=C, C=N). ^1H NMR (600 MHz, CDCl_3 , δ , ppm): 10.14 (s, 1H, CH=N), 8.71 (d, 1H, $J_{3,4'} = 8.0$ Hz, $\text{H}_{\text{arom.-}4'}$), 8.41 (d, 1H, $J_{7,8'} = 8.0$ Hz, $\text{H}_{\text{arom.-}8'}$), 8.28 (d, 1H, $J_{5,6'} = 8.0$ Hz, $\text{H}_{\text{arom.-}5'}$), 8.24 (t, 1H, $J_{6,7'} = 8.0$ Hz, $\text{H}_{\text{arom.-}7'}$), 8.08 (t, 1H, $J_{5,6'} = 8.0$ Hz, $\text{H}_{\text{arom.-}6'}$), 8.03 (s, 1H, $\text{H}_{\text{pyrimid.-}5}$), 7.47 (d, 1H, $\text{H}_{\text{arom.-}3'}$), 4.80 (s, 3H, OCH_3). ^{13}C NMR (150 MHz, CDCl_3 , δ , ppm): 186.5 ($\text{C}_{\text{pyrimid.-}6}$), 171.6 (C-OH), 161.3 ($\text{C}_{\text{pyrimid.-}2} + \text{CH=N}$), 157.3 ($\text{C}_{\text{pyrimid.-}4}$), 133.8, 129.5, 129.1, 127.1, 126.9, 125.0 ($\text{C}_{\text{arom.-}8'}$), 109.8 ($\text{C}_{\text{pyrimid.-}5}$), 102.8 ($\text{C}_{\text{arom.-}2'}$), 54.8 (OCH_3).

4-(((4-Chloro-6-methoxypyrimidin-2-yl)imino)methyl)benzene-1,2-diol (8): From 3,4-dihydroxy-benzaldehyde 5 (152 mg). Yield: 230 mg (82%). M.p.: 133-136 °C. FT-IR (KBr, ν , cm^{-1}): 3446 (OH), 3030-3016 (CH-aro.), 2958 (CH-alip.), 1661-1587 (C=C, C=N). ^1H NMR (600 MHz, $\text{DMSO-}d_6$, δ , ppm): 9.70 (s, 1H, CH=N), 7.28 (dd, 1H, $J_{2,6'} = 2.0$ Hz, $J_{5,6'} = 8.0$ Hz, $\text{H}_{\text{arom.-}6'}$), 7.24 (d, 1H, $\text{H}_{\text{arom.-}2'}$), 7.06 (br s, 2H, $\text{H}_{\text{pyrimid.-}5} + \text{OH}$), 6.91 (d, 1H, $\text{H}_{\text{arom.-}5'}$), 6.10 (s, 1H, OH), 3.82 (s, 3H, OCH_3). ^{13}C NMR (150 MHz, $\text{DMSO-}d_6$, δ , ppm): 171.4 ($\text{C}_{\text{pyrimid.-}6}$), 163.4 ($\text{C}_{\text{pyrimid.-}4}$), 160.3 ($\text{C}_{\text{pyrimid.-}2} + \text{CH=N}$), 152.7 (C $_4$ -OH), 146.4 (C $_3$ -OH),

129.3 ($\text{C}_{\text{arom.-}1'}$), 125.0 ($\text{C}_{\text{arom.-}6'}$), 116.0 ($\text{C}_{\text{arom.-}2'}$ + $\text{C}_{\text{arom.-}5'}$), 115.0 ($\text{C}_{\text{pyrimid.-}5}$), 54.1 (OCH_3).

N-(Benzo[d][1,3]dioxol-5-ylmethylene)-4-chloro-6-methoxypyrimidin-2-amine (9): From piperonal 6 (165 mg). Yield: 210 mg (72%). M.p.: 192-194 °C. FT-IR (KBr, ν , cm^{-1}): 3425 (OH), 3065-3020 (CH-aromatic), 2890 (CH-aliphatic), 1660, 1594 (C=C, C=N). ^1H NMR (600 MHz, $\text{DMSO-}d_6$, δ , ppm): 9.81 (s, 1H, CH=N), 7.54 (dd, 1H, $J_{2,6'} = 2.0$ Hz, $J_{5,6'} = 8.0$ Hz, H-6'), 7.32 (d, 1H, H-4'), 7.13 (d, 1H, H-7'), 6.17 (s, 1H, $\text{H}_{\text{pyrimid.-}5}$), 6.09 (s, 2H, CH_2), 3.92 (s, 3H, OCH_3). ^{13}C NMR (150 MHz, $\text{DMSO-}d_6$, δ , ppm): 171.4 ($\text{C}_{\text{pyrimid.-}6}$), 163.4 ($\text{C}_{\text{pyrimid.-}4}$), 160.3 ($\text{C}_{\text{pyrimid.-}2} + \text{CH=N}$), 153.2 (C-7a'), 148.9 (C-3a'), 129.0 (C-5' + C-6'), 109.0 (C-7'), 106.7 (C-4'), 102.8 ($\text{C}_{\text{pyrimid.-}5}$), 94.7 (CH_2), 54.1 (OCH_3).

3. Results and discussion

3.1. Chemistry

Treatment of 2-amino-4-chloro-6-methoxypyrimidine (3) with three aldehyde derivatives (2-hydroxy-1-naphthaldehyde (4), 3,4-dihydroxybenzaldehyde (5) and piperonal (6) in ethanol and catalytic amount of glacial acetic acid under reflux afforded the desired imine derivatives 7-9 in 77, 82 and 72% yield, respectively (Scheme 1).

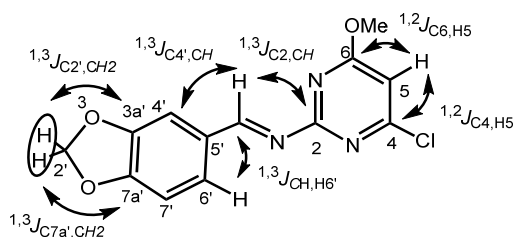
The structure of compounds 7-9 was confirmed by the ^1H , ^{13}C and 2D NMR spectra. In the ^1H NMR spectra of compounds 7-9, the singlets at δ 10.14, 9.70 and 9.81 ppm were assigned for the imino protons (CH=N), whereas the singlets at δ 8.03, 7.06 and 6.17 ppm, were attributed to H-5 of the pyrimidine ring, respectively. The aromatic protons were fully analyzed where H-3', H-4', H-5' and H-6' of the analogue 7 appeared as doublets at δ 7.47 ($J_{3,4'} = 8.0$ Hz), 8.71, 8.28 ($J_{5,6'} = 8.0$ Hz) and 8.08 ppm, respectively. H-7' appeared as a triplet at δ 8.24 ppm ($J_{6,7'} = 8.0$ Hz), while H-8' was resonated as a doublet at δ 8.41 ppm ($J_{7,8'} = 8.0$ Hz). Moreover, the aromatic protons H-2' and H-5' of the analogue 8 appeared as doublets at δ 7.24 ($J_{2,6'} = 2.0$ Hz) and 6.91 ppm ($J_{5,6'} = 8.0$ Hz), respectively. H-6' of the same analogue resonated as a doublet of doublets at δ 7.28 ppm, while the singlet at δ 6.10 ppm was attributed to the hydroxyl group. The analogue 9 showed two doublets at δ 7.32 ($J_{2,6'} = 2.0$ Hz) and 7.13 ($J_{5,6'} = 8.0$ Hz) ppm were assigned for the aromatic protons H-2' and H-6', respectively. H-7' appeared as a doublet of doublets at δ 7.54 ppm ($J_{2,6'} = 2.0$ Hz, $J_{5,6'} = 8.0$ Hz), while the methylene protons (CH_2) appeared as a singlet at δ 6.09 ppm. The methoxy group at C-6 of the pyrimidine ring of compounds 7-9 was resonated as singlets at δ 4.80, 3.80 and 3.90 ppm, respectively. In the ^{13}C NMR spectra of compounds 7-9, the resonances at δ 161.3 and 160.3 ppm were assigned for the pyrimidine carbon atom 2 together with the carbon atom of the imino group, respectively. The carbon atoms 4 of the analogues 7-9 were resonated at δ 157.7 and 163.4 ppm, respectively, while C-5 of the same scaffold appeared at δ 109.3, 115.0 and 102.8 ppm, respectively. C-6 of the pyrimidine ring appeared at δ 186.5, 171.4 and 171.4 ppm, respectively, whereas the methoxy group resonated at δ 54.8 and 54.1 ppm, respectively.

Table 1. Antibacterial activity of the Schiff-base derivatives of pyrimidine.

Compound	Conc., $\mu\text{g/mL}$	Diameter of inhibition zone in mm for different microbial species																	
		<i>S. aureus</i>			<i>E. coli</i>			<i>B. cerus</i>			<i>Salmonella</i>			<i>Pseudomonas</i>			<i>Klebsella</i>		
		100	200	300	100	200	300	100	200	300	100	200	300	100	200	300	100	200	300
7	-	-	-	7	10	15	8	10	12	-	13	15	-	-	-	-	-	-	-
8	-	-	-	6	8	10	-	-	10	-	8	10	-	-	-	-	-	-	-
9	-	-	-	-	8	10	-	-	-	-	-	-	-	-	-	-	-	-	10

Table 2. Antifungal activity of the Schiff-base derivatives of pyrimidine.

Compound	Conc., $\mu\text{g/mL}$	Diameter of inhibition zone in mm for different microbial species								
		<i>C. albicans</i>			<i>C. tropicalis</i>			<i>A. fumigates</i>		
		100	200	300	100	200	300	100	200	300
7	-	-	8	11	8	10	12	8	10	11
8	-	-	-	-	-	8	10	-	6	10
9	-	-	-	-	8	9	10	-	-	-

**Figure 2.** J_{CH} Correlations in the HMBC NMR spectrum of compound 9.

The aromatic carbon atom (C-OH) of the analogue 7 appeared at δ 171.6 ppm, while those of the analogue 8 (C₄-OH), (C₃-OH) were resonated at δ 152.7, 146.4 ppm, respectively. Furthermore, the aromatic carbon atom C-2' of compound 7 appeared at δ 102.8 ppm in addition to the resonances at δ 133.8-125.0 ppm were assigned to the rest aromatic carbon atoms. The aromatic carbon atoms C-1' and C-6' of compound 8 appeared at δ 129.3 and 125.0 ppm, respectively, whereas C-2' together with C-5' of the same compound were resonated at δ 116.0 ppm. Compound 9 showed resonances at δ 129.0 ppm assigned for the aromatic carbon atoms C-1' together with C-7', while the signals at δ 106.7, 149.9, 153.2 and 109.2 ppm were attributed to the aromatic carbon atoms C-2', C-2a', C-5a' and C-6', respectively. In addition, the methylene Carbon atom appeared at δ 94.7 ppm. Compound 9 has been selected for further NMR study. The gradient-selected ^1H , ^{13}C , HMBC NMR spectrum [36] of compound 9 revealed two $^{1,2}J_{CH}$ in addition to five $^{1,3}J_{CH}$ correlations. Thus, the imino proton (CH=N) at δ 9.81 ppm showed three $^{1,3}J_{CH}$ correlations: first one with C-2 of the pyrimidine ring at δ 160.3 ppm, the second correlation with the aromatic carbon atom C-6' at δ 129.0 ppm and the last one with the aromatic carbon atom C-4' at δ 106.7 ppm. Two $^{1,3}J_{CH}$ correlations between CH₂ protons at δ 6.09 ppm with C-3a' and C-7a' at δ 148.9 and 153.2 ppm, respectively, were observed. Furthermore, H-5 of the pyrimidine ring at δ 6.17 ppm showed a $^{1,2}J_{CH}$ correlation with C-4 of the same ring at δ 163.4 ppm as well as a $^{1,2}J_{CH}$ correlation with C-6 at δ 171.4 ppm (Figure 2).

3.2. Antibacterial and antifungal activity

The synthesized compounds 7-9 were screened *in-vitro* for their antibacterial activity against bacteria: *Staphylococcus aureus*, *Escherichia coli*, *Bacillus cerius*, *Salmonella*, *Klebsella* and *Pseudomonas aeruginosa* using the disc-agar diffusion technique [37]. Muller Hinton agar was used as culture media for antibacterial activity. The antifungal activities were tested against fungus: *Candida albicans*, *Candida tropicalis* and *Aspergillus fumigates* by diffusion method. Recommended concentrations 100, 200 and 300 $\mu\text{g/mL}$ of the test samples in DMSO solvent was introduced in the respective method. Petri

plates containing 20 mL of Mueller Hinton Agar were used for all the used bacteria. *Candida albicans* strain was cultivated in Sabouraud's dextrose agar. Sterile Whatman No.1 filter paper disks (6 mm in diameter) impregnated with the solution in dimethylsulfoxide of the test was placed on the Petri plates. A paper disc impregnated with DMSO was used as negative control. The plates were incubated for 24 h in the case of bacteria and 72 h for fungi at 28 °C. The inhibition zone diameters were measured in millimeters using a caliper vernia.

The results of the antibacterial activity are shown in Table 1 and antifungal activity is shown in Table 2. It is observed that the activity of compounds increases with an increase in the concentration of the solutions. The antibacterial activity of all synthesized compounds showed no activity against *S. aureus* and *Pseudomonas* but all compounds showed good antibacterial activity against *E. coli* and *Salmonella* for compound 7 and 8 compounds, Table 1.

The results of antifungal activity of all synthesized compounds showed good active against *C. tropicalis*. Compounds 7 and 8 showed moderate activity against *A. fumigatus*, as shown in Table 2.

4. Molecular modeling analysis

The molecular docking was performed using SYBYL-X 1.1 and the docking results were shown by PyMOL [38]. Our molecular docking analysis of the new analogues based on the modeling study which was performed to understand the binding mode of these analogues with the aspartate aminotransferase (ATT) of *E. coli* [39] binding pocket (PDB code: 3DLG, [40]).

Compound 9 has been selected for the docking modeling study, since its binding energy score -8.2, indicating a selectivity of substituted olefinic benzoate in its binding to the enzyme pocket (Figure 3). As shown in Figure 3, the aromatic ring of compound 9 was fitted into an aromatic rich subpocket surrounded by the aromatic side chains of Trp130, in addition to two hydrogen bondings. The pyrimidine backbone was located in the middle of the binding pocket, anchoring the oxygen atom of the methoxy group at C-6 in a favourable position for hydrogen bonding with the NH₂ group of Arg280,

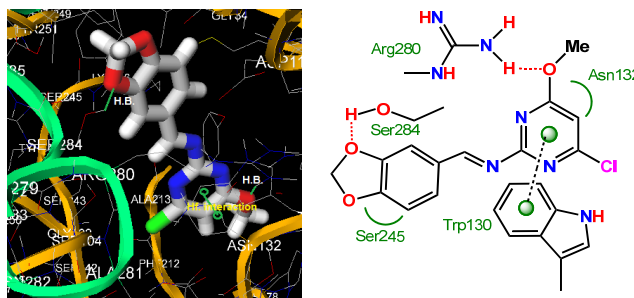


Figure 3. Docked conformation of compound 9. Docked conformation of compound 9 showing two hydrogen bondings: Arg280 with oxygen atom of methoxy group at C-6 of pyrimidine ring and Ser284 with oxygen atom of piperonal ring. It exhibited also hydrophobic interaction between phenyl group of the pyrimidine scaffold moiety and Trp130 of aspartate transaminase enzyme residues of *E. coli*.

in addition to a hydrogen bonding between the oxygen atom of piperonal group with OH of Ser284 of the aspartate amino transferase (AAT) enzyme. Overall, the combination of hydrophobic interaction and π -stacking appears to govern the binding of compound 9 with AAT of *E. coli*.

5. Conclusion

In conclusion, synthesis of new aryl 1-(4-chloro-6-methoxypyrimidin-2-yl)imine derivatives (7-9) has been described. All the new synthesized compounds have been evaluated for their antibacterial as well as antifungal activities. Compounds 7 exhibited potential activity against *B. cereus* at 100 $\mu\text{g/mL}$, whereas the others analogues showed moderate to poor activity. In addition, compound 7 showed a moderate antifungal activity against *C. tropicalis* and *A. fumigates* at 100 $\mu\text{g/mL}$. Compound 9 has been selected for a molecular modeling study showing its binding to the aspartate aminotransferase (AAT) of *E. coli* enzyme pocket through two hydrogen bondings and one hydrophobic interaction.

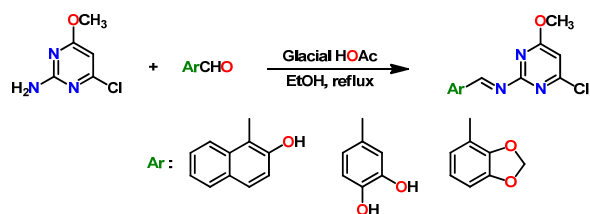
Acknowledgement

We are grateful to Miss Anka Friemel of chemistry department, University of Konstanz, Germany are highly acknowledged for the NMR experiments. We are also grateful to Departments of Physiology and Microbiology, College of Veterinary Medicine, Basrah University, Iraq for providing the facilities.

References

- Jain, K. S.; Chitre, T. S.; Miniyar, P. B.; Kathiravan, M. K.; Bendre, V. S.; Veer, V. S.; Shahane, S. R.; Shishoo, C. J. *Curr. Sci.* **2006**, *90*, 793-803.
- Patel, D. H.; Mistry, B. D.; Desai, K. R. *Indian J. Hetero. Chem.* **2003**, *13*, 179-180.
- Bantawal, S. H.; Manjathuru, M.; Mari, K. S.; Padiyath, K. M. *Bioorg. Med. Chem.* **2006**, *14*, 2040-2047.
- Sharma, P.; Rane, N.; Gurram, V. K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4185-4190.
- Adnan, A. B.; Hesham, T. Z.; Sherif, A. F.; Azza, M. B. *Eur. J. Med. Chem.* **2003**, *38*, 27-36.
- Russell, R. K.; Press, J. B.; Rampulla, R. A.; McNally, J. J.; Falotico, R.; Keiser, J. A. *J. Med. Chem.* **1988**, *31*, 1786-1793.
- Cocco, M. T.; Congiu, C.; Lilliu, V. *Bioorg. Med. Chem.* **2006**, *14*, 366-372.
- Heidelberger, C.; Chaudhuri, N. K.; Danneberg, P.; Mooren, D.; Griesbach, L.; Duschinsky, R.; Schnitzer, R. J.; Plevin, E.; Scheiner, J. *Nature* **1957**, *179*, 663-666.
- Beattie, J. F.; Breault, G. A.; Ellston, R. P. A.; Green, S.; Jewsbury, P. J.; Midgley, C. J.; Naven, R. T.; Minshull, C. A.; Pauptit, R. A.; Tucker, J. A.; Pease, J. E. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2955-2960.
- Kimura, H.; Katoh, T.; Kajimoto, T.; Node, M.; Hisaki, M.; Sugimoto, Y.; Majima, T.; Uehara, Y.; Yamori, T. *Anticancer Res.* **2006**, *26*, 91-97.
- Lagoja, I. M. *Chem. Biodiver.* **2005**, *2*, 1-50.
- Dudhe, R.; Sharma, P. K.; Verma, P.; Chaudhary, A. J. *Adv. Sci. Res.* **2011**, *2*, 10-17.
- Yamazaki, Y.; Takahashi, M.; Todome, Y. *Proc. Soc. Exp. Biol. Med.* **1970**, *133*, 674-677.
- Prichard, M. N.; Quenelle, D. C.; Hartline, C. B.; Harden, E. A.; Jefferson, G.; Frederick, S. L.; Daily, S. L.; Whitley, R. J.; Tiwari, K. N.; Maddry, J. A.; Secrist, J. A.; Kern, E. R. *Antimicrob. Agents Chemother.* **2009**, *53*, 5251-5285.
- Miyasaka, T.; Tanaka, H.; Baba, M.; Hayakawa, H.; Walker, R. T.; Balzarini, J.; De Clercq, E. *J. Med. Chem.* **1989**, *32*, 2507-2509.
- Tanaka, H.; Takashima, H.; Ubasawa, M.; Sekiya, K.; Nitta, I.; Baba, M.; Shigeta, S.; Walker, R. T.; De Clercq, E.; Miyasaka, T. *J. Med. Chem.* **1992**, *35*, 337-345.
- Balzarini, J.; Baba, M.; De Clercq, E. *Antimicrob. Agents Chemother.* **1995**, *39*, 998-1002.
- Fillios, L. C.; Naito, C.; Andrews, S.; Roach, A. M. *Circ. Res.* **1960**, *8*, 71-77.
- Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937-6963.
- Kreutzberger, A.; Burgwitz, K. *Arch. Pharm.* **1981**, *314*, 394-398.
- Monge, A.; Martinez-Merino, V.; Sanmartin, C.; Fernandez, F. J.; Ochoa, M. C.; Bellver, C. Artigas, P. *Arznei-Forschung* **1990**, *40*, 1230-1233.
- Weitzel, K. W.; Wickman, J. M.; Augustin, S. G.; Strom, J. G. *Clin. Ther.* **2000**, *22*, 1254-1267.
- Yang, W.; Ruan, Z.; Wang, Y.; Van Kirk, K.; Ma, Z.; J. Arey, B.; Cooper, C. B.; Seethala, R.; Feyen, J. H. M.; Dickson, J. K. *J. Med. Chem.* **2009**, *52*, 1204-1208.
- Gillespie, R. J.; Bamford, S.; Botting, R.; Comer, M.; Denny, S.; Gaur, S.; Griffin, M.; Jordan, A. M.; Knight, A. R.; Lerpiniere, J.; Leonardi, S.; Lightowler, S.; McAteer, S. et al. *V. J. Med. Chem.* **2009**, *52*, 33-47.
- Tanaka, F.; Takeuchi, S.; Tanaka, N.; Yonehara, H.; Umezawa, H.; Sumiki, Y. *J. Antibiot.* **1961**, *14*, 161-162.
- Reddick, J. J.; Saha, S.; Lee, J.; Melnick, J. S.; Perkins, J.; Begley, T. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2245-2248.
- Stenbuck, P.; Hood, H. M. 1962, US Patent 3, 049, 544.
- Brogden, R. N.; Carmine, A. A.; Heel, R. C.; Speight, T. M.; Avery, G. S. *Drugs* **1982**, *23*, 405-430.
- Hughes, W. T.; Feldman, S.; Sanyal, S. K. T. *Can. Med. Assoc. J.* **1975**, *112*, 47-50.
- Hertel, L. W.; Border, G. B.; Kroin, J. S.; Rinzel, S. M.; Poore, G. A.; Todd, G. C.; Grindey, G. B. *Cancer Res.* **1990**, *50*, 4417-4422.
- Mayer, T. U.; Kapoor, T. M.; Haggarty, S. J.; King, R. W.; Schreiber, S. L.; Mitchison, T. J. *Science* **1999**, *286*, 971-974.
- Sharp, D. J.; Rogers, G. C.; Scholey, J. M. *Nature* **2000**, *407*, 41-47.
- Parikh, K. S.; Vyas, S. P. *Asian J. Biochem. Res.* **2012**, *2*, 1-7.
- Gulcan, M.; Sonmez, M.; Berber, I. *Turk. J. Chem.* **2012**, *36*, 189-200.
- Kalpesh, S. P.; Sandip, P. V. *der Pharm. Lett.* **2012**, *4*, 638-640.
- Davis, A. L.; Keeler, J.; Laue, E. D.; Moskau, D. J. *Magn. Reson.* **1992**, *98*, 207-216.
- Abraham, E. P.; Chain, C. M.; Fletcher, A. D.; Gardner, N. G.; Heatly, M. A.; Jennings, H. W. *Lancet* **1941**, *238*, 177-1989.
- Seeliger, S.; de Groot, B. L. J. *Comput. Aid. Mol. Des.* **2010**, *24*, 417-422.
- Onuffer, J. J.; Ton, B. T.; Kleent, I.; Kirsch, J. F. *Protein Sci.* **1995**, *4*, 1743-1749.
- Zhan, P.; Liu, X.; Li, Z.; Fang, Z.; Pannecouque, C.; De Clercq, E. *Chem. Biodivers.* **2010**, *7*, 1717-1727.

Graphical Abstract



It is very important to confirm the author(s) last, middle and first names in order to be displayed correctly on our website as well as in the indexing databases.

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